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## (54) METHOD OF MAKING CROSSLINKED POLYMER MATRICES IN TISSUE TREATMENT APPLICATIONS

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# (56) References Cited

#### U.S. PATENT DOCUMENTS

3,619,371	11/1971	Crook et al
3,742,955	7/1973	Battista et al
3,788,948	1/1974	Kegadal et al
3,810,473	5/1974	Cruz Jr. et al
3,876,501	4/1975	Cruz, Jr. et al
3,949,073	4/1976	Daniels et al
3,960,830	6/1976	Bayer et al
4,002,531	1/1977	Royer .
4,055,635	10/1977	Green et al
4,088,538	5/1978	Schneider .
4,101,380	7/1978	Rubinstein et al
4,164,559	8/1979	Miyata et al
4,179,337	12/1979	Davis et al
4,192,021	3/1980	Deibig et al
4,238,480	12/1980	Sawyer .

(List continued on next page.)

### FOREIGN PATENT DOCUMENTS

2134744	5/1995	(CA).
0013249	1/1980	(EP) .
0042253	12/1981	(EP).
0154447	9/1985	(EP) .
0157359	10/1985	(EP).
0171176	2/1986	(EP) .
0243179	10/1987	(EP).
0330389	8/1989	(EP) .
2628634	9/1989	(EP).
0341007	11/1989	(EP).

0431479 <b>A</b> 1	6/1991	(EP) .
0466383	1/1992	(EP) .
0575273	12/1993	(EP).
0640647	3/1995	(EP) .
0656214	6/1995	(EP) .
0656215	6/1995	(EP) .
0680990	11/1995	(EP) .
0732109	9/1996	(EP) .
4-227265	4/1990	(JP) .
60-70972	3/1994	(JP) .
7-090241	4/1995	(JP) .
WO 84/01106	3/1984	(WO).
WO 85/04412	10/1985	(WO).
WO 87/04078	7/1987	(WO).
WO 90/05755	5/1990	(WO).
WO 94/01483	1/1992	(WO).
WO 92/13025	8/1992	(WO).
WO 92/13578	8/1992	(WO).
WO 94/03155	2/1994	(WO).

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#### OTHER PUBLICATIONS

Poly(Eethylene Glycol) Chemistry: Biotechnical & Biomedical Applications, Chapter 22, J. Milton Harris, Ed., Plenum Press, NY (1992).

Abuchowski et al. (1977), "Alteration of immunological properties of bovine serum albumin by covalent attachment of polyethylene glycol," *Biol. Chem.* 252(11):3578–3581. Abuckowski et al. (1984), "Cancer therapy with chemically modified enzymes. I. Antitumor properties of polyethylene glycol–asparaginase conjugates," *Cancer Biochem. Biophys.* 7:175–186.

Abuckowski et al. (1977), "Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase," *J. Biol. Chem.* 252(11):3582–3586. Anderson et al. (1964), "The use of esters of n-hydroxysuccinimide in peptide synthesis," [???] 86:1839–1842.

(List continued on next page.)

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#### (57) ABSTRACT

Crosslinked polymer compositions comprise a first synthetic polymer containing multiple nucleophilic groups covalently bound to a second synthetic polymer containing multiple electrophilic groups. The first synthetic polymer is preferably a synthetic polypeptide or a polyethylene glycol that has been modified to contain multiple nucleophilic groups, such as primary amino (-NH<sub>2</sub>) or thiol (-SH) groups. The second synthetic polymer may be a hydrophilic or hydrophobic synthetic polymer which contains, or has been derivatized to contain, two or more electrophilic groups, such as succinimidyl groups. The compositions may further comprise other components, such as naturally occurring polysaccharides or proteins (such as glycosaminoglycans or collagen) and/or biologically active agents. Also disclosed are methods for using the crosslinked polymer compositions to effect adhesion between a first surface and a second surface; to effect tissue augmentation; to prevent the formation of surgical adhesions; and to coat a surface of a synthetic implant.

# 12 Claims, 18 Drawing Sheets